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Early summer meningo-encephalitis in Lower Austria, 1956-1958.
Epidemiology and clinic in the epidemic area of Neunkirchen.

by H. Moritsch and J. Krausler.

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(1959).

In the early summer of 1927, Schneider, for the first time, observed an illness of the central nervous system (CNS) among his patients at the medical department of the Neunkirchen hospital, which he considered a separate disease on the basis of his clinical and epidemiological observations, and which he initially designated as "meningitis serosa epidemica" (32). He found additional evidence in the following years that seemingly confirmed his hypothesis of an infection sui generis; and yet it was spring 1956 before a neurotropic viral strain was isolated from the brain of a fatal case of encephalomyelitis, which was identified as the pathogen of the CNS infection first described by Schneider, and designated early summer meningo-encephalitis (ESME) strain by serologic typing.

From this point on, systematic investigations were conducted in this district into the dissemination of ESME, partial results of which have already been reported (19,23,24). The present paper is designed to convey a summary of all results obtained in the past three years (1956-1958).

These investigations cover all patients that had contracted a questionable viral infection of the CNS during this period and had been referred to Neunkirchen Hospital by all practising physicians for treatment and isolation due to suspicion of poliomyelitis. The area served by the hospital is almost identical with the political district of Neunkirchen, so that the number of admitted patients gives a true picture of the morbidity conditions -- at least for this district. The district of Neunkirchen is located in the eastern part of Lower Austria, covers 1,146 km² and contains 90,000 inhabitants.

Epidemiological investigations.

into the distribution of ESME were conducted in 1953 in the neighboring Steiermark (38,40), substantiating the occurrence of this infectious disease in other areas of Eastern Austria, confirmed later by personal findings in large portions of Lower Austria (24). In addition, reports of the isolation of this virus or the occurrence of this disease have come from other parts of Europe, i.e. Sweden (43), Finland (26), East Prussia (35), Poland (30,36), Czechoslovakia (6), Hungary (12),

Yugoslavia (4,18,21,41), Bulgaria (27), Roumania (9) and Russia (35), known also as tick encephalitis, Central European encephalitis, biphasic milk encephalitis or Kumlinge disease.

The first virologic findings

are credited to Russian researchers who were able to isolate neurotropic strains of virus in the Far East as early as 1937; this disease was initially called Far Eastern encephalitis or Taiga encephalitis and seems to be fairly common in Russia (35). It cannot be decided whether a uniform symptomatology or a consistent type of pathogen are involved, especially since clinical, epidemiological and virologic-serological examinations have revealed diverse variants, e.g. the Ural variant (31) and Konan variant (13), in addition to a distinction between the clinical appearance of tick encephalitis and milk encephalitis, based on the suspected portal of entry. However, all cases involve pathogens with a related antigenic structure, as found also in the strains isolated in Central Europe (28,29). This antigenic structure was also demonstrated for the virus of louping ill (7,8) in serologic investigations by Casals and Webster.

Louping ill has been observed in Northern England and Scotland since the end of the 18th century and does not seem to affect man as in the case of ESME virus (except for laboratory infections), but only sheep. Special significance must therefore be attached to findings by Likar and Dane, who recently observed symptomatology in humans resembling poliomyelitis whose pathogen was found to be in etiological correlation with the virus of the louping ill group. (22).

Aside from these specifically neurotropic properties of ESME or the viral types belonging to this group, there exist antigenically related viral types which, however, produce the clinical picture of the hemorrhagic fever type and do not cause infections of the human CNS. While the pathogens of the hemorrhagic fever of Omsk (20) and Kyasanur Forest disease (42) should be included in this category, the pathogens of the hemorrhagic fever in the Astrachan region, the Crimea (44) and in Bulgaria (2) seem to have an antigenic structure different from that of ESME virus.

Personal investigations.

Virologic-serological research included attempts to isolate the virus as well as demonstration of specific antibodies in the patient's serum.

In contrast to the entero-viruses, the ESME virus is not eliminated with the stool, so that the practitioner is dependent primarily on parts of the CNS obtained during autopsies. Isolation of the "Scharl" strain succeeded once (1956), whereas all other attempts at isolation failed, including those from blood and liquor.

The complement fixation reaction and the neutralization test are suited for serologic diagnosis. Both methods were used repeatedly in the course of the illness, since blood was drawn from all patients once a week for at least 4 weeks.

The complement fixation reaction (CFR) was started with an antigen obtained according to Casals from infected mouse brains, in three concentrations with decreasing serum dilutions. Fixation occurred at 4°C overnight and readings were taken one hour after addition of the hemolytic system (37°C). For purposes of economy, the entire starting material of the CFR was later treated with only 0.6 ml instead of the customary 1.5 ml, without detriment to the results.

The neutralization test was carried out only qualitatively with concentrated serum and a viral concentration of 20-100 LD₅₀ $\bar{a}\bar{a}$ (corresponds to a dilution 10⁻⁶ of the supernatant of a fresh mouse brain passage). Fixation occurred after 1 hour at room temperature and 2-3 hours at 4°C; the serum-virus mixture was then injected subcutaneously into 4-5 mice (8-10 g) and observed for 21 days.

In the evaluation of serologic test results, the two-phase course of the disease must be considered (exactly as in poliomyelitis), i.e. the start of the organism's immunization must be timed with the commencement of viremia (= phase 1), which, in our experience, is to be effected about 12 days before the appearance of meningitis (see Fig. 1), so that the demonstration of neutralizing antibodies may be expected already at the manifestation of the first characteristic symptoms, i.e. at the start of phase 2. Complement fixing antibodies, on the other hand, are demonstrable much later (see table 1). According to present experience, neutralizing antibodies are still positively demonstrable in the serum at least 3 years after infection, whereas complement fixing antibodies cannot be shown in a serum dilution of 1:4 as early as 6 months post infectionem.

On the basis of these serologic tests, more than half of all cases (see table 2) with suspected viral infection of the CNS in the district of Neunkirchen were identified as ESME infections.

The clinical course of the disease must also be considered from the viewpoint of the two-phase character of the infection (see Fig. 1).

The development of this initial phase, which is also called acquired illness after Bieling, is quite variable with individual patients and generally lasts 2-4 days. The overwhelming majority of cases complain of fatigue, headache, inflammatory processes of the nasal and pharyngeal mucosa as well as of the ocular conjunctiva, accompanied by temperature elevations to 38°C; however, these symptoms may be so poorly defined that the patients do not consider them extraordinary. Following an afebrile interval, or growing directly out of the catarrhal stage, the second phase of infection develops after an average of 8 days.

The second phase of ESME occurs in three clinical forms:

1. meningitis, 2. meningo-encephalitis, 3. meningo-encephalitis with paralyses.

In the majority of cases the inception is sudden, marked by severe head and backache, temperature elevation up to 40°C and stiffness of the neck. It is usually accompanied by vertigo and vomiting, less often by diarrhea.

1. The meningeal form is usually called "meningitis serosa" by the clinician and distinguishes itself by its benign and rapid course; the overwhelming majority of cases heal in 3-5 days without discomfort.

2. The meningo-encephalitic form presents, in addition to manifestations of meningeal irritation, dullness of the sensorium, delirious interference with sleep, hyperkinesia with spasms, particularly in the facial musculature, short-termed disturbances of sensibility at the trunk and the extremities, as well as paralyses of the ocular muscle. The reflexes are usually normal, but isolated irregularities in reflex action occur in the form of hyperreflexes. This meningo-encephalitic symptomatology lasts for 7-10 days and generally heals without complications. Occasionally, vegetative disturbances such as persistent headaches or heightened irritability, are recorded. One youthful patient manifested a psychotic condition during the encephalitis, which was resolved within 6 months by specific psychiatric treatment. Two other patients (55a, 61a) developed the symptoms of parkinsonism.

3. The third form of this illness is identical with the classic course of poliomyelitis acuta anterior and cannot be differentiated clinically. The foreground is occupied by the well-known sign of paralysis in the extremities, observed in 5 patients. This paralysis affected the shoulder zone musculature 3 times and the femoral muscles once, whereas both areas were affected in one patient. Two patients died; one of them with signs of Landry's paralysis. The remaining 3 patients regained the use of their muscles after about six months, although two retained the effects of atrophy.

ESME reveals a special peculiarity in the form of so-called late paralyses. They occur without a rise in temperature about 5-10 days after defervescence, especially in the shoulder zone musculature, usually preceded by disturbances in the affected areas' sensibility. In spite of initial, distinctly noticeable atrophy, the affected muscles undergo a rapid recovery, usually resulting in restitutio ad integrum.

The development of the three clinical forms of phase 2 seems to depend essentially on the patient's age. As table 3 indicates, younger persons can expect a meningeal course, whereas the encephalitic form can be anticipated principally from age 40 to 60. The 5 cases with paralyses are distributed with absolute regularity on the 40th to 90th year of life; but, relatively speaking, susceptibility to paralysis rises distinctly with advancing age — despite the small number of cases.

Diagnosis.

In addition to the determination of all clinical symptoms, lumbar puncture is of primary importance in hospital diagnosis. The cytologic examination of the liquor usually shows only a cell increase up to 400/3 cells. The qualitative examination of cells in the liquor reveals predominantly lymphocytes. The protein content increases with the duration of illness. The liquor's sugar values are always normal.

Occasionally, a small portion of cases shows pathological forms of EKG in addition to the changes in the liquor; this may be interpreted as sequelae of myocarditis. These changes are repaired in all cases after 6-8 weeks, however.

The lungs sometimes show slight catarrhal manifestations, while the liver and spleen are normal in most cases.

Examination of the blood during the first phase usually shows leukopenia with relative lymphocytosis, while the leukocyte readings of the blood are slightly higher in the second phase. The sedimentation rate of the blood cells may also have higher values.

Therapy.

A specific therapy in the form of gamma globulins (obtained from convalescent serum after ESME) is occasionally credited with success (1,31,33,43). On the other hand, since the serum of our own cases revealed neutralizing antibodies in sufficient concentration at the start of phase 2 (25), no great improvement can be expected from additional supplies of specific antibodies, based on theoretical considerations alone. We have no personal experience in this matter.

Pathologic-histological findings

were obtained from 4 patients only owing to the low mortality. Whereas two older patients (62 and 83 years) died in the paralytic stage, the two younger cases (26 and 54 years) involved meningo-encephalitides. Histologic examination revealed predominantly small round-cellular-glious infiltrates with primarily perivascular arrangement, being especially pronounced in the basal ganglia, in the cerebellum and the grey substance of the spinal cord, as found also after infections with polio virus. A differential diagnostic delineation of these two viral infections solely on the basis of simple histologic examinations is not yet possible for this reason (*).

(*) Concerning histologic differential diagnosis, reference is made to a paper by K. Jellinger and W. Povac, "Contribution to the neuropathology of early summer meningo-encephalomyelitis" (in print), in Schweiz. Z. Path. Bakt.

Epidemiology.

Due to the similarity between ESME and poliomyelitis in the clinical course and pathol.-histol. findings, special significance is attached to epidemiological investigations, since they offer essential differentiation of the two infections in this respect. While poliomyelitis occurs everywhere in all of Europe, ESME seems to be limited to certain regions. Thus, in Austria, ESME is localized in the area along the eastern and southern borders, and has not penetrated westward at this writing. However, since these districts also report (virologically verified) cases of poliomyelitis, Coxsackie type A and B, as well as ECHO type IX infections in addition to endemic ESME, it seems indicated to initiate promising comparisons between ESME and the other infections with respect to localization, season and infective mode.

In investigations of the geographic dissemination of ESME infections which, in our research, are always confronted with all other infections of the central nervous system, it is apparent that aggregations of ESME (e.g. Aspang) and of other infections (e.g. Puchberg) exist in isolated locales, although there are relatively large communities (Ternitz, Pottschach and Gloggnitz), especially in the valley west of Neunkirchen, in which both infections have been recorded --- at least in local proximity (Fig. 2). This tabulation shows essentially that other infection of the CNS must be expected in the endemic region of ESME, although a reciprocal influence in the sense of an exclusion of one or the other infection certainly is not indicated.

In contrast to geographic confrontation, seasonal distribution of the cases shows a distinct delineation of ESME from the other infections (see Fig. 3). Whereas ESME dominates absolutely from May to July and plays a numerically subordinate role in the remaining months, the "other" infections of the CNS prefer the midsummer and late summer months.

Thus, in the first half of the years 1956-1958, 37 cases of ESME are opposed by 9 infections of other genesis, although the monthly maximum of ESME is admitted in July. In July, however, other infections of the CNS are also noted in increasing numbers, resulting in an annual ratio of 28 cases of ESME to 10 other infections. In the second half of the year the so-called other infections predominate, with a conspicuous double-peaked rise in August and November. This probably indicates an inconsistent etiology of this group of diseases that occur in aggregates in different seasons, and are diagnosed as poliomyelitis, Coxsackie and ECHO infections based on control examinations of liquor and stools (19,24). The peculiar seasonal accumulations of ESME, repeatedly stressed also by other authors, has caused us to designate this disease as early summer meningo-encephalitis (ESME), since this term characterizes this widely disseminated and variously named infectious disease far better than allusions to its suspected mode of transmission (e.g. tick encephalitis, milk encephalitis) or geographic locale (e.g. Far Eastern encephalitis, Taiga encephalitis, Central European encephalitis, etc.), all of which only convey the idea of a local dissemination.

Mode of infection.

The seasonal occurrence of ESME alone offers clues to the infective mode in man. Two possibilities have been listed so far: 1. The bite of infected ticks (especially *Ixodes ricinus* and *Ixodes persulcatus*) and 2. the consumption of the unboiled (virus-containing) milk of goats and sheep, but also of cows. Originally, only the bite of infected ticks was blamed for transmission to man, and the high percentage of tick bites on patients as well as the isolation of the virus from ticks were offered as proof thereof.

However, the concept of an oral infection via virus-containing milk has recently gained in importance, after it had been demonstrated experimentally that the viremic stage is followed by secretion of virus in the milk of externally quite healthy animals (15,39). Moreover, the infection of such a widely distributed food brings the possibility of an epidemic-like eruption of this disease which normally occurs only sporadically in this country. Heretofore only one such epidemic has been reported, resulting in over 600 cases following the consumption of fresh goat and cow milk at Roznava (Czechoslovakia) in 1951 (5).

It was noted during the interrogation of our own cases that part of the patients admitted a tick bite or the consumption of fresh milk during the suspected incubation time, but that another part negated the same with high credibility (see tab. 4). We therefore feel ourselves justified in the conclusion that, independent of all previous opinions, there may be other possibilities of a human infection not considered to date.

In the study of this problem, it should be remembered that the viral reservoir must be searched for among wild and domestic animals, from which the infection is transmitted to man directly or via arthropods as vectors. The extent of this natural virus reservoir is only vaguely suggested by isolation of the virus from mice (10,17) and ducks (6) and demonstration of neutralizing antibodies in the serum of mice and shrews (3), singing birds (11), bats (16), sheep and goats (23,34,38) as well as cows, deer, rabbits and chickens (38), since these investigations can only be credited with a spot check from the entire "biota." Still, this leads to the conclusion that the virus must be rather widely disseminated in nature and possesses a corresponding number of chances for contact with human beings.

Concerning the conditions in the district of Neunkirchen with about 4,400 goats and sheep, and about 24,000 cows, neutralizing antibodies were found in sheep and goats. Comparative examinations of the biota in regions free of ESME are planned and could give clues to the relation between virus reservoir and chances of human infection. We were unable to obtain a positive indication of the cause of the localized dissemination of ESME in the district of Neunkirchen or the east and southeast of Austria, especially since the biota of these areas seemingly does not differ from that of other regions of Austria in which ESME has not yet been demonstrated.

These as yet unexplained conditions of infection in the animal kingdom and transmission of the virus to man are contrasted by the untested findings that infections from man to man have not occurred. The virus was not demonstrable either in the stool of patients or, upon systematic examination, in the stool or urine of infected goats (14), pointing to a basically different path of viral contagion compared to poliomyelitis, for instance. In this connection a comparative study of differentiable sensitivity of various viral strains to sodium-desoxycholate merits special attention, since the known viral types excreted with the stool, e.g. poliomyelitis, encephalomyocarditis, Theiler virus, proved resistant, whereas all viruses transmitted by arthropods, including a Russian ESME strain, were particularly sensitive and became inactive in a sodium-desoxycholate dilution of 1:1,000 after 1 hour at 37°C (37).

This inability of the ESME virus to excrete with the stool also means the end of a natural infective chain, since further infections emanating from sick or convalescing persons need not be feared, nor has this process been observed in practice. At the same time, the initiation of isolating measures normally undertaken in connection with diseases of the central nervous system transmissible from man to man (e.g. poliomyelitis), becomes unnecessary.

Summary.

Systematic investigations in the district of Neunkirchen during the period 1956-1958 led to the diagnosis of early summer meningo-encephalitis (ESME) in 89 cases (= 55%) of meningitis and meningo-encephalitis (partly with paralyses) among 162 patients with questionable viral infections of the CNS. ESME has a concentrated incidence in May to July and has clinical similarities with polio-virus infections. The differentiation of the two diseases, however, is possible only by means of aimed virologic-serological examinations (identification of the pathogen, CFR). Wild and domestic animals represent the natural viral reservoir; human infections cannot be explained completely by tick bites or the consumption of fresh milk, however. A direct infection from man to man does not occur.

Illustrations and tables.

Tab. 1. Determination of the time (day of illness) of demonstration of antibodies against ESME in the patient serum.

		Referred to			
		phase 1		phase 2	
CFR	earliest	-	7	-	7
	latest	14	21	7	14
	arithmetic average	39	45	22	30
		27.8	35.0	18.2	24.5
Neutralization test		?	9	0	1

Tab. 2. Proportion of ESME among the CNS infections at Neunkirchen Hospital 1956-1958.

Year	Total	Of these, ESME	Percentage
1956	80	44	55%
1957	53	31	58%
1958	29	14	48%
	162	89	55%

Tab. 3. Breakdown of viral infections of the CNS 1956-1958.

	ESME virus			Other viruses		
	MS	ME	MEP	MS	ME	MEP
0-10	8	-	-	12	2	4
11-20	7	5	-	15	4	-
21-30	5	3	-	9	5	1
31-40	6	5	-	5	2	1
41-50	9	14	1	-	2	-
51-60	4	14	1	3	4	-
61-70	-	3	1	-	3	-
71-80	-	-	1	-	1	-
81-90	-	-	1	-	-	-

MS = meningitis serosa, ME = meningo-encephalitis
MEP = meningo-encephalitis with paralyzes.

Tab. 4. Results of the interrogation of patients with ESME concerning tick bites and consumption of fresh milk.

Year	Total cases	Ticks			Fresh goat's milk		Fresh cow's milk	
		yes	?	no	yes	no	yes	no
1956	44	18	8	16	not done		not done	
1957	31	8	8	15	8	23	not done	
1958	14	4	2	8	2	12	3	9